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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER
HUTSON, RICHARD G

ART UNIT	PAPER NUMBER
1652	

DATE MAILED: 03/26/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/656,309	Applicant(s) CALLEN ET AL.	
	Examiner Richard G Hutson	Art Unit 1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 December 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-51* is/are pending in the application.

4a) Of the above claim(s) *1-30 and 43-51* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *31-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on 9/11/00 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 3 .
4) ☒ Interview Summary (PTO-413) Paper No(s). 11 .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Claims 1-51 are at issue and are present for examination.

Election/Restrictions

Applicant's election of Group IV, Claims 31-42, drawn to a method of generating a variant of a nucleic acid which encodes a polymerase, in Paper No. 10, 12/4/2001, is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-30 and 43-51 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention. Election was made without traverse in Paper No. 10.

Priority

Applicants statement on the first line of the specification reciting that this application is a continuation-in-part application of co-pending U.S. Patent Application Serial Number 09/391,340, filed September 7, 1999, which is a divisional of U.S. Patent Application Serial No. 08/907,166, filed August 6, 1997, now issued as U.S. Patent No. 5,948,666 is acknowledged.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Applicants filing of information disclosures, Paper No. 3, filed 12/18/2000, is acknowledged. Those references considered have been initialed. It is brought to applicants attention that reference "AA", U.S. Patent No. 4,165,188, entitled "Ribbon Mask and Guide for Dot Matrix Impact Printers", appears to be unrelated to the subject matter of the instant application but has been considered.

Drawings

Applicants filing of informal drawings is acknowledged, however, these have been reviewed by the Draftsperson and are acceptable.

Specification

The disclosure is objected to because of the following informalities:

On page 1, line 2 of the specification, applicants recite "Application Serial **Number** 09/391,340..." and on line 3 applicants recite "U.S. Patent Application Serial **No.** 08/907,166..." It is suggested that applicants refer to "Number" consistently throughout the specification (i.e. Number, No. etc...).

On page 3, line 24 of specification applicants recite "...SEQ ID **No**:2...", whereas all other references to SEQ ID NOs recite "..SEQ ID **NO**:..." It is suggested that applicants maintain consistency through out the application and refer to "..SEQ ID NO: 2..."

On page 5, line 21, "detecting..." is indented. This is not the beginning of a paragraph, thus it is unclear as to why this indention occurs.

On page 18 applicants recite "...in the 5' to 3 sequence..." This should be "...in the 5' to 3' sequence..."

Appropriate correction is required.

Claim Objections

Claim 32 is objected to because of the following informalities:

Claims 32 recites the method "GSSM". As discussed below under 112 2nd paragraph rejection it is unclear what method of modification "GSSM" refers to. It is suggested that the first time an abbreviation is used in a claim for a term that is not well understood, that the abbreviated term be written out in full, followed by its abbreviation in parenthesis.

Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 32 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 32 is indefinite in that it is confusing in that the claim is drawn to a method of generating a variant wherein the modifications are introduced by a method selected from a group of methods known to one of ordinary skill in the art, with the exception of "GSSM". It is unclear what applicants intend by the recitation "GSSM".

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 31, 32, 35 and 42 are rejected under 35 U.S.C. 102(b) as being anticipated by Gelfand et al. (U.S. Patent No. 5,491,086, issued 2/13/1996).

Gelfand et al. teach a purified thermostable nucleic acid polymerase and DNA coding sequences from *Pyrodictium* species. Gelfand specifically teach a nucleic acid from *P. occultum* (SEQ ID NO: 3) which is substantially identical to instantly disclosed SEQ ID NO: 1, as "substantially identical" is defined in the instant disclosure as two or more nucleic acid sequences that have at least 60% nucleotide identity (See page 14, lines 17-24 of specification) and SEQ ID NO: 3 disclosed by Gelfand is 66.5% identical to instantly disclosed SEQ ID NO: 1. Gelfand et al. further teach a method of

generating a variant comprising obtaining the disclosed nucleic acid sequence (SEQ ID NO: 3) which is substantially identical to SEQ ID NO: 1 and modifying one or more nucleotides in said sequence (See Example 7, column 28). Specifically, Gelfand et al. constructed *P. oc* polymerase genes lacking 3'-5' exonuclease activity using site-directed mutagenesis by overlap extension PCR using oligonucleotides, to alter the nucleotides for codons Asp 187 and Glu 189 to code for alanine (See Example 7, column 28).

Thus, Gelfand anticipate a method of generating a variant comprising obtaining a nucleic acid comprising a sequence substantially identical to SEQ ID NO: 1 and modifying one or more nucleotides in said sequence to another sequence (claim 31), wherein the modifications are introduced by oligonucleotide-directed mutagenesis (claims 32 and 35) or site-specific mutagenesis (claims 32 and 42) (See Example 7, column 28).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 31-34 and 36-41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Gelfand et al. (U.S. Patent No. 5,491,086, issued 2/13/1996), in view of Short (U.S. Patent No. 5,939,250, filed 5/22/1996).

Claim 31 and 32 are included in this 103 rejection to the extent that they clearly encompass the methods with the limitations of claims 33, 34, 36, 37, 38, 39, 40 and 41, wherein said modifications are introduced by the specifically claimed methods. These particular embodiments of claims 31 and 32 are not anticipated although as discussed above, claims 31 and 32 also embrace embodiments which are anticipated. Thus both the 102 and 103 rejections are proper.

Claims 33, 34, 36, 37, 38, 39, 40 and 41 are drawn to a method of generating a variant comprising obtaining a nucleic acid comprising a sequence substantially identical to SEQ ID NO: 1 and modifying, deleting or adding one or more nucleotides in said sequence to another nucleotide, wherein the modifications are introduced by error-prone PCR (claim 33), shuffling (claim 34), assembly PCR (claim 36), sexual PCR mutagenesis (claim 37), in vivo mutagenesis (claim 38), cassette mutagenesis (claim 39), recursive ensemble mutagenesis (claim 40), and exponential ensemble mutagenesis (claim 41).

As discussed above, Gelfand et al. teach a purified thermostable nucleic acid polymerase and DNA coding sequences from *Pyrodictium* species. Gelfand et al. further teach a method of generating a variant comprising obtaining the disclosed nucleic acid sequence (SEQ ID NO: 3) which is substantially identical to SEQ ID NO: 1 (as "substantially identical" is defined in the instant disclosure as two or more nucleic acid sequences that have at least 60% nucleotide identity, page 14, lines 17-24 of specification) and modifying one or more nucleotides in said sequence. Gelfand et al. further teach that the entire coding sequence of the DNA polymerase gene is not

required to produce a biologically active gene product with DNA polymerase activity and the availability of the disclosed DNA encoding the *Pyrodictium* DNA polymerase sequence provides the opportunity to modify the coding sequence (by modification of the nucleotide sequence) so as to generate a mutant protein also having DNA polymerase activity. Gelfand et al. teach that unlike *Taq* DNA polymerase and native *Tth* polymerase, the disclosed *Pyrodictium* DNA polymerase has a 3'-5' exonuclease activity, that is generally considered desirable, but can increase non-specific background amplification during PCR. For the purpose of illustration of the invention, Gelfand et al. teach a method of constructing *P. occultum* polymerase genes lacking 3'-5' exonuclease activity using site-directed mutagenesis by overlap extension PCR to alter the nucleotides for codons Asp 187 and Glu 189 to code for alanine. Gelfand et al. while teaching a means of generating a variant comprising obtaining a nucleic acid sequence substantially identical to SEQ ID NO: 1 and modifying one or more nucleotides in said sequence do not teach the specific means of mutagenesis selected form the group consisting of "error-prone PCR", "shuffling", "assembly PCR", "sexual PCR mutangenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis" and "exponential ensemble mutagenesis"

Short teaches a number of known techniques for directed mutagenesis for the development of modified enzymes with particularly desired properties that are absent or less pronounced in the wild-type enzyme, such as stability to heat or organic solvents. Short specifically teaches "error-prone PCR", "shuffling", "assembly PCR", "sexual PCR

mutangenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis" and "exponential ensemble mutagenesis".

Each of the above references are analogous art because they are each involved in field of mutagenesis of a protein sequence.

One of ordinary skill in the art at the time of filing would have been motivated to modify the nucleic acid sequence encoding the *Pyrodictium* DNA polymerase taught by Gelfand et al. using each of the methods taught by Short, including "error-prone PCR", "shuffling", "assembly PCR", "sexual PCR mutangenesis", "in vivo mutagenesis", "cassette mutagenesis", "recursive ensemble mutagenesis" and "exponential ensemble mutagenesis" in order to modify the amino acid sequence of the *Pyrodictium* DNA polymerase such that the enzyme has a reduced 3'-5' exonuclease activity relative to the wild-type enzyme. Further motivation to the ordinary skilled artisan for such methods of generating variants of the taught *Pyrodictium* DNA polymerase encoding nucleic acid would be to increase other properties of the encoded polymerase such as processivity, ability to incorporate unconventional nucleotides, thermostability, or stability to organic solvents (these later two enzyme properties are suggested by Short). One of ordinary skill in the art at the time of filing would have a reasonable expectation of success because of the high level of knowledge in the field of nucleic acid mutagenesis and the teachings of Gelfand et al. who successfully generated a variant of the *Pyrodictium* DNA polymerase encoding nucleic acid using similar mutagenesis methods. It is noted that as the rejected claims are not limited to the isolation or

identification of a variant with a specific property, but merely to a method of generating a variant, the reasonable expectation of success is high.

Thus Gelfand et al. and Short make obvious claims 31, 32, 33, 34, 36, 37, 38, 39, 40 and 41 drawn methods of generating a variant comprising obtaining a nucleic acid comprising a sequence substantially identical to SEQ ID NO: 1 and modifying, deleting or adding one or more nucleotides in said sequence to another nucleotide, wherein the modifications are introduced by error-prone PCR (claims 31-33), shuffling (claims 31, 32 and 34), assembly PCR (claims 31, 32 and 36), sexual PCR mutagenesis (claims 31, 32 and 37), in vivo mutagenesis (claims 31, 32 and 38), cassette mutagenesis (claims 31, 32 and 39), recursive ensemble mutagenesis (claims 31, 32 and 40), or exponential ensemble mutagenesis (claims 31, 32 and 41).

Remarks

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Richard G Hutson whose telephone number is (703) 308-0066. The examiner can normally be reached on 7:30 am to 4:00 pm, M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapy Achutamurthy can be reached on (703) 308-3804. The fax phone numbers for the organization where this application or proceeding is assigned

are (703) 305-3014 for regular communications and (703) 305-3014 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Richard Hutson, Ph.D.
Patent Examiner
Art Unit 1652
March 25, 2002